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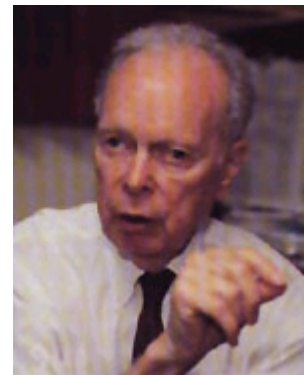
## INTERVIEW

### An Interview With Dr. Denham Harman

*Free radicals are atoms or atomic groups that contain unpaired electrons. Since electrons have a very strong tendency to exist in a paired rather than an unpaired state, free radicals rather indiscriminately pick up electrons from other atoms, converting those other atoms into secondary free radicals, and thus setting up a chain reaction that can cause substantial biological damage.*

*Dr. Denham Harman, M.D., Ph.D., first proposed a theory of aging as the indiscriminate chemical reactivity of free radicals possibly leading to random biological damage. His idea has met with much experimental success, and is now considered a major theory of aging. The theory implies that antioxidants such as vitamins E and C, which prevent free radicals from oxidizing (removing electrons from) sensitive biological molecules, will slow the aging process. Dr. Harman launched his theory by showing, for the first time, that feeding a variety of antioxidants to mammals was able to extend their life spans.*

*In 1970, he founded the American Aging Association (AGE), an organization of biomedical research scientists bent on understanding and slowing the aging process. Dr. Harman is a researcher at the University of Nebraska Medical Center, and is also a co-founder of the International Association of Biomedical Gerontology.*



*Dr. Harman, interviewed for Life Extension magazine by Greg Fahy, Ph.D., reminisces on the early days of his research, and suggests future courses of study to more fully understanding the aging process . . . and how to stop it.*

### The Antioxidant Pioneer

**Denham Harman**, Life Extension magazine scientific advisory board member, is the originator of the free-radical theory of aging and pioneered research with antioxidants. He is a true anti-aging pioneer.

Life Extension: Could you briefly recount how you decided to start the American Aging Association (AGE), and some of the early events in setting up AGE?

Denham Harman: A bunch of us were sitting around at the meeting in 1969 of the International Association of Gerontology. We realized at that time there were less than 300 people in the Gerontological Society who were in the biological science section, and less than 100 were doing any work. That was of immediate concern to us. We also were bemoaning the fact that, if you went and spoke with the average person about aging, he thought about old people. It never crossed their minds how you got old, which was something else.

In New York the following summer, there were maybe four, five or six meetings held where we decided to do something. We had the inaugural luncheon at the Waldorf Astoria hotel that fall. The first meeting was held in 1971, just ahead of the Gerontological Society meeting in Houston.

It's been an interesting experience. It's very difficult to get scientists to agree on anything, but I would think at least we might agree on the matter of money. Because if you're going to have to compete with the sociologists and so forth, you're going to get a fraction of the money. They're going to take most of it. I wouldn't mind that, except it's not

doing anything in terms of what really needs to be done. One of the sociologists was bemoaning the fact that she thought too much money was being given to the biologists!

**LE:** I understand that you wanted the American Aging Association to be like the March of Dimes, but for aging instead of for birth defects.

**DH:** Oh, I don't know. The idea was a forum where scientists could get together and speak with one voice, and have a greater impact on Congress, say, and also try to educate the people about aging research, and educate the physicians about what could be done. There's no point in doing this work if you don't transfer it to doctors and transfer it to you and me.

**LE:** What do you think the most pressing need is in this field today?

**DH:** (Laughs) We just need tremendous help. It's absolutely ridiculous. Did you see the book that came out a few years ago-from the National Academy of Medicine-in which they advocated increasing the support for aging research to a billion dollars a year? Most of the research was going in support of more social studies. This is one of my bones of contention. When groups like the members of the Gerontological Society talk about aging research, to them aging research is all the social programs they want demonstrations for. But you could fund every social worker, and they won't make one dent on this major problem. They're taking, I guess, two-thirds of the money from the National Institute on Aging.

**LE:** What's the total amount of money that's actually spent on biomedical aging research?

**DH:** I figure it's \$25 million to \$50 million. Probably closer to \$25 million.

**LE:** That would be only, what, a 20th of the NIA budget?

**DH:** Whatever, it's a small fraction. Yet I can't get the scientists to stick together. That was one of the reasons for forming the American Aging Association in the first place, so we'd have a place where scientists could associate, so to speak, have a bigger voice. But instead of that, we have a drop of sand here, a drop of sand there, and nobody's talking with a single voice.

**LE:** Could you recount for us some of the events leading up to your idea that free radicals might be important in aging?

**DH:** At the time, I was a research chemist for Shell Development Co., working in the reaction kinetics department, which is basically free radical chemistry. I became interested in aging, but I hadn't made any connection whatsoever between free radical chemistry and aging. I thought about free radicals only in terms of straight chemistry. I was working at that time on free radical reactions involved with oxygen and organic compounds, sulphur compounds, phosphorous compounds-that sort of thing. It was interesting chemistry.

**LE:** What peaked your interest in aging?

**DH:** I came home from work one night and my wife showed me a magazine article by William Lawrence, who at that time was a science editor for The New York Times. It was entitled, "Tomorrow You May Be Younger," but it was a very well written article about the work of Dr. Bogomolets at the Gerontology Research Center in Kiev, Russia. Anyway, it was an interesting article. I didn't understand what he was talking about. I didn't even know some of the vocabulary, but it was interesting.

**LE:** What was the general gist of it?

**DH:** Trying to increase life span, that sort of thing.

**LE:** This would have been when?

**DH:** December of 1945. While in medical school I was intrigued by some things I learned. I took a psych course in the department of biochemistry and cancer, and I also became aware of the work by Carrel at Rockefeller University on chicken cells. [Editor's note: This was a famous series of experiments that seemed to show that cells could divide without limit in tissue culture; they seemed to be, in effect, immortal.] And I felt sure there was something haywire with that experiment, because the human experience is that everything dies. It was subsequently shown that they were actually inadvertently transferring new cells into that old bunch.

Anyway, I sat down and asked the question, What is the cause of aging? I thought, Mother Nature finds something that works, and uses it over and over again with variations on the theme. So I thought that since aging was universal, since everything aged and died, there should be one common cause that was modifiable by genetics and by environment. So that was the premise on which I was looking at this problem.

It's only when I look back that I realized I was in somewhat of a unique situation. I had a B.S. and Ph.D. in chemistry and had about 15 years work in laboratories, the last seven years on my own. I had just finished a superb course in biology at medical school and an internship. But it was like looking for a needle in a haystack. Nothing meshed. Everything I could think of went exactly nowhere. I was just about ready to give up on the whole thing. I felt like I was wasting my time. But you hate to give up-you think there's something there, but you're just not bright enough to see it.

So anyway, I was sitting at the desk in my office one morning and it suddenly dawned on me-free radicals flashed through my mind. You know you have the answer, but you don't know how you got there, but that was it.

**LE:** When was this, as nearly as you can figure?

**DH:** This was the first part of November 1954. I had finished my internship at the end of June. In the first part of December, I wandered around the Berkeley campus talking to people to get their reaction to this idea. They said it's interesting, but just too simple to explain a complex problem like aging. I tried to explain that free radical chemistry only looked simple, that it was far more complex than that. Anyway, I didn't make much headway, with the exception of two people. They were both organic chemists who were doing some biological work-one was a virologist and one was a photosynthesist. And they said, Yeah, maybe there's something there.

We first started looking at catalase because of the connection with the Fenton reaction [an iron-catalyzed free radical generation reaction that does not require living systems to work]. Somebody over at the physics department had built an EPR [an electron paramagnetic resonance spectrometer, a device for detecting free radicals], but I couldn't detect free radicals with that system. I also did a number of studies trying to modify this system, and studies with catalase activity, but nothing came of it.

**LE:** You were just trying to find free radicals in living systems at this point?

**DH:** Yes.

**LE:** Did you have an idea that free radicals would increase with age or did you think that it was just a constant onslaught that would eventually overwhelm the organism? Did you have an idea as to how free radicals would participate in aging?

**DH:** I knew, for example, that in radiation biology, if the free radical level was high enough, you could kill an animal. We worked on several things at the same time. Most of the work was on life span studies. We used AJR and C3H mice, relatively short-lived strains, but we were dealing with a very complex system. The idea was that free-radical reactions were involved in aging, and that if you could decrease the level, you might be able to increase life span. You give an antioxidant to an animal, it's taken in and distributed to the tissues. Where in the tissues it goes, to what part of the cell, we didn't know.

**LE:** What agents did you choose? Was that the 2-MEA [2-mercaptoethylamine] study?

**DH:** 2-MEA was chosen because that compound was synthesized by the Atomic Energy Commission as a radiation protection compound. It is a very effective compound.

**LE:** How did you pick your dose?

**DH:** Maybe this had to do with something in a radiation study. I don't recall exactly. We were just lucky. In terms of life span, we might easily have had too much or too little. It seems to me that when we went above 1 percent [in the diet], we would get in trouble. Anyway, we used 2-MEA, we used ascorbic acid, we used cysteine, and we used hydroxylamine once in a later study. Knowing what I know now, I wish I could go back and do that hydroxylamine study again. I'd use different concentrations and also some different hydroxylamine molecules.

**LE:** When you published your first study showing that MEA could extend life span, did that suddenly change a lot of people's thinking? Did that drastically increase interest in this area or did you find that people still resisted your idea?

**DH:** I was essentially talking to myself for about 10 years. The biologists at that time knew very little chemistry, certainly nothing about free radical chemistry, but it was vice versa with the chemists. The first life span study was presented as an abstract at the American Federation of Clinical Research. I think it was in 1956 or 1957 in Carmel, Calif. There was gradual interest. Then in the mid 1960s it started to increase further, and when the SOD business [the discovery of superoxide dismutase, a natural enzyme that destroys superoxide free radicals in the body] came out in 1969, it took off.

We gradually accumulated a lot of data in the mid-1960s that showed, yes, we increased the average life expectancy, which is what I expected to see. But I did not see such an increase that I could really be sure, in terms of maximum life span. On that basis, the question came up, is the failure to increase maximum life span because the theory is wrong or because it should be modified? I kind of concluded it should be modified, and I wrote a small paper that was published in the April issue of The Journal of the American Geriatrics Society in 1972. The title was, "The Biologic Clock: The Mitochondria?" I followed it up subsequently with a paper in 1983, I think, which was published in AGE, called "The Free Radical Theory of Aging: the Consequences of Mitochondrial Aging."

There is a great deal of work going on today in that area, but at that time, I didn't know a lot about mitochondria, per se. But it didn't take much imagination to figure that your DNA or your membranes could be subject to free radical attack. So basically, the paper suggested that free radicals generated by the mitochondria would kill us, so to speak.

At any rate, right now, I think what's important, aside from the past history, is that there's a growing consensus that aging changes are induced by free radical reactions, largely initiated by the mitochondria, and that the rate of damage to the mitochondria determines our life span. I think that's the essence. People still disagree with it. But the point is that people have been going in so many different directions that a lot of people could not be brought to bear on one subject. I think that is changing now.

**LE:** Certainly, the free radical theory has inspired more research than any other concept in aging, there's no question about that. There are more data related to that theory than on any other subject in aging. Most facts are consistent with the theory.

**DH:** Well, I think you have to actually accept that at some point in time you establish a fact, and maybe we're reaching that point now. Probably, we're past that point, or past the point when something which is called a theory becomes a fact and you just take it as such.

**LE:** One thing that I think will help is to establish how a given level of oxidant stress governs life span.

**DH:** Are you familiar with the work on pigeons that was done here by Sohol and also by Barjillian in Madrid, Spain? He showed that pigeons divert a smaller fraction of the oxygen they consume to the superoxide radical. They suggest, and I think this is correct, that this is the same thing as food restriction. On the one hand, you're cutting down free radical initiation rates genetically, and on the other you're doing it by decreasing your consumption of substrate. Almost certainly the people who work on the senescence-accelerated mouse have shown that the peroxidation is much higher in that mouse than in the longer-lived mouse.

**LE:** How far do you think can we go? What is the expectation as to how far we can push out the life span by an absolutely optimum approach to dealing with free radical damage?

**DH:** Who knows? Free radical reactions are almost impossible to stop. You can slow them up, and that depends on how good you are. You can cut down on initiation of free radicals by the mitochondria and then you use some antioxidants to scavenge the rest of them. Nobody can answer your question.

From a practical standpoint, I think today we're reaching a point where we can actually intervene in the aging process and increase our functional life span and probably also the maximum life span. And that's where I think we are today. If you and I are around 100 years from now, we can debate what we do from there, but right now the immediate thing is to try to do something about where we are at the moment.

**LE:** You have also been a geriatrician in the background all these years, but we never hear about that. What can you tell us about your own practice?

**DH:** I can't remember exactly when this was, but sometime probably in the 1970s they needed some help over in the Douglas County Hospital, and so the chairman said, 'You're interested in aging, we need someone to go over there and do some work, so you're it.' Very crudely, that was about it. So until four years ago, I was taking care of geriatric

patients. I'd put it like this: it was interesting, but also somewhat depressing, because a lot of these people were Alzheimer's disease patients, and there was not much you could do.

**LE:** What supplements do you recommend?

**DH:** I would recommend that adults take a gram to a gram and a half of vitamin C a day. I'd also recommend they take vitamin E. Many, many people are taking at least 400 IU a day.

**LE:** Do you think 400 IU of vitamin E would be the target dose, the best?

**DH:** I don't know. The thing you have to worry about is that you don't do any damage. The trouble is, we've had experience with single doses of things like vitamin E that were used for years and years, but we don't know what is the long-term effect of taking a variety of antioxidants at levels which you think individually are fine. But some may be too much.

**LE:** What about the role of selenium supplementation?

**DH:** Well, again nobody really knows. I take 100 micrograms a day, on the average, and 25,000 IU every other day of beta-carotene. When I say these things, I realize perfectly well I really don't know for sure that these are the optimum. I just don't know the optimum. At least, I think these are reasonably safe amounts to take. And I take some vitamin B6 and I take magnesium.

**LE:** Any differences in the need for antioxidants between men and women?

**DH:** I'm interested in trying to find out if there are any data on the effects of antioxidants on pregnancy. I would like to see women, by and large, get a great deal more antioxidants than they're getting. We might be able to get at this indirectly by giving it to women who have been diagnosed as having Down syndrome. These women oftentimes will want to keep the baby rather than having it aborted, and maybe they could be given an option, if they want to do it, and see if they'll take an increase in antioxidants: vitamin E, C and beta-carotene, for example.

Theoretical data are suggesting that the major factor in Alzheimer's disease of the sporadic late onset type-that's 90 to 95 percent of Alzheimer's cases-is a mutation in earlier life that affects mitochondrial function, either a mutation of mitochondrial DNA or of nuclear DNA that influences mitochondrial function. In essence, it looks as though at least this large category of Alzheimer's disease cases is a mitochondrial disorder. It's not simply in the brain, it's a widespread disorder, involving platelets, fibroblasts, etc.

**LE:** Some Alzheimer's patients have language-use differences in their 20s.

**DH:** Yes, and this indicates that the problem started way back. If this is the case, then we can make the argument that women should take more antioxidants.

Dr. Steven B. Harris, M.D., assisted with this interview

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without first consulting your physician.